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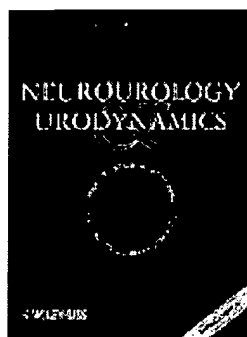
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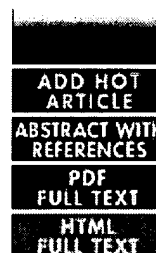
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## Original Basic Science Article

# Preliminary results of myoblast injection into the urethra and bladder wall: A possible method for the treatment of stress urinary incontinence and impaired detrusor contractility

Michael B. Chancellor<sup>1\*</sup>, Teruhiko Yokoyama<sup>1</sup>, Sean Tirney<sup>1</sup>, Carol E. Mattes<sup>1</sup>, Hideo Ozawa<sup>1</sup>, Naoki Yoshimura<sup>2</sup>, William C. de Groat<sup>2</sup>, Johnny Huard<sup>3</sup>
<sup>1</sup>Division of Urologic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

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- Pittsburgh Tissue Engineering Initiative

**Keywords**

myoblast; bladder; urethra; urodynamics; incontinence; gene therapy; tissue engineering

**Abstract**

The purpose of this study is to explore the feasibility of myoblasts, the precursors of muscle fibers, injected periurethrally as a potential treatment of stress urinary incontinence. We also studied myoblast injection into the bladder wall to potentially improve detrusor contractility. A myoblast cell line was transduced with adenovirus carrying the expression of the  $\beta$ -galactosidase reporter gene while in culture. The cells were incubated with fluorescent latex microspheres (FLMs) to follow the outcome of the injected cells. The tissue was harvested 3-4 days after injection; sectioned, fixed, assayed for  $\beta$ -galactosidase expression, and counterstained with H+E. Photographs of the slides were taken under

light and fluorescence microscopy. We have noted a large number of cells expressing  $\beta$ -galactosidase and containing FLMs in the urethral and bladder walls under fluorescent microscopy (8 animals). Many regenerative myofibers expressing  $\beta$ -galactosidase were also seen in the urethral and bladder walls. The fusion of injected myoblasts to form myotubes was seen in both the urethral and bladder walls. The introduction of myoblasts into the urethral and bladder wall is feasible and results in formation of myotubes and myofibers in the smooth muscle layers of the lower urinary tract. We hypothesize that myoblast injections can be used as a non-allergenic agent to enhance urethral closure and bladder function. *Neurourol. Urodynam.* 19:279-287, 2000. © 2000 Wiley-Liss, Inc.

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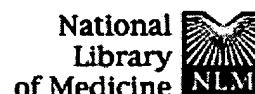
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## Nitric oxide mediated erectile activity is a testosterone dependent event: a rat erection model.

Zvara P, Sioufi R, Schipper HM, Begin LR, Brock GB.

Lady Davis Institute for Medical Research Department of Urology  
Montreal, Quebec, Canada.

Classically, androgens were thought to be linked to sexual activity in man through their action on increased libido. Recently, the sex hormone dependent nature of nitric oxide synthase (NOS), the enzyme system producing the neurotransmitter of erection (nitric oxide) has been reported. Our study evaluated how changes in testosterone levels alter erectile function. In forty-seven rats the erectile response to cavernous nerve electrostimulation was recorded 1, 5, 10, 20 and 30 d post-bilateral orchiectomy, and compared to controls. Penile tissue was subsequently stained for the presence of NOS, using an NADPH diaphorase technique. Forty eight rats were used in part two. After orchiectomy exogenous testosterone was administered and the erectile function as well as density of NOS positive nerve fibers was assessed. All castrated animals showed a rapid decrease in serum free testosterone levels within 24 h. In contrast, a gradual decrease in intracavernous pressure was recorded with cavernous nerve stimulation, proportional to the time post orchiectomy. NADPH diaphorase staining showed a decreased density of nonadrenergic noncholinergic (NANC) nerve fibers innervating the cavernosal tissue proportional to the time post orchiectomy. With reconstitution of the androgen milieu the erectile response returned to near normal values and recovery of NADPH-positive nerve fibers was observed. Based on presented data we conclude that testosterone or a metabolite plays a direct role in erection acting



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testosterone or a metabolite plays a direct role in erection acting through an effect on nitric oxide synthase within the corpora cavernosa.

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## **Role of nitric oxide in penile erection.**

**Jung HC, Mun KH, Park TC, Lee YC, Park JM, Huh K, Seon DH, Suh JK.**

Department of Urology, School of Medicine, College of Pharmacy  
Yeungnam University, Taegu, Korea.

The present study was undertaken to investigate the role of nitric oxide (NO) in erectile physiology by correlating its action with the existence and activity of nitric oxide synthase (NOS), which produces NO. We applied Western blot analysis in both human and rat penile tissue. In the rat, reduced nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase staining and spectrophotometric assay were also performed, in addition to in vivo electroerection study with pharmacological manipulation. Western blot analysis identified a protein of 155 KDa identical to the neural form of NOS in the human and rat penis. The NOS blot densities in the two species were similar, and both were lower than that in the rat cerebellum. Histochemical staining localized NOS to neurons innervating the corpora cavernosa, including the pelvic plexus, the cavernosal nerves and their terminal fibers within the corporeal erectile tissue, and dorsal penile nerves. NOS activity was also found in the cerebellum, urethra, penis, and urinary bladder, in decreasing order of intensity. Intracavernous injections of NOS inhibitor (L-NOARG or L-NAME in concentrations from  $10^{-6}$  M to  $10^{-3}$  M) suppressed electrostimulation-induced erection in a concentration-dependent manner. Subsequent intracavernous injection of L-Arginine ( $10^{-2}$  M) partially restored the erection. The neural form of constitutive NOS in the corpora cavernosa synthesizes NO, which mediates penile erection. Determination of cavernosal NOS expression or activity may permit characterization of certain pathological conditions that

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**Delayed testosterone replacement restores nitric oxide synthase-containing nerve fibres and the erectile response in rat penis.**

**Baba K, Yajima M, Carrier S, Morgan DM, Nunes L, Lue TF Iwamoto T.**

Department of Urology, University of California San Francisco, California, USA.

**OBJECTIVE:** To elucidate the effect of testosterone on penile innervation. **Materials and methods** Three groups of six rats each were assessed; two groups (1 and 2) were castrated and the third (group 3) underwent a sham operation (control). Eight weeks after castration, group 2 received a subcutaneous injection with testosterone. At 8 weeks, the rats in group 1 and 3 underwent a final functional analysis while those in group 2 did so at 12 weeks. The evaluation included a subcutaneous injection with apomorphine to study centrally mediated erection, and cavernosal nerve electrostimulation and papaverine injection to study peripherally mediated erection. At death a penile mid-shaft specimen was taken for NADPH-diaphorase staining. **RESULTS:** In the apomorphine study, castration resulted in significantly fewer yawns and erections than in the control, and those in group 2 significantly better central erectile function than in the controls. The mean (SEM) number of nitric oxide synthase (NOS)-containing nerve fibres in the corpora cavernosa and both dorsal nerves of castrated rats, at 46.2 (9.1) and 203 (32.1), respectively, were significantly lower than in rats in group 2, at 84.1 (11.2) and 300.6 (17.1), and than in the controls, at 88.6 (10.9) and 306.3 (22.9), respectively. The intracavernosal pressure decreased significantly in the absence of testosterone, both after electrostimulation and intracavernosal papaverine injection. However, there was no difference between the control and group 2 rats in either the number of NOS-containing nerve fibres or in the

peripheral erectile functional study. **CONCLUSIONS:**  
Testosterone acts on the nervous system to mediate erection; when it is absent there may be down-regulation of both the production and activity of NO, thereby decreasing the response to peripheral stimulation via the NO pathway. The restoration of erectile function seen in rats in group 2 supports this phenomenon. Delayed testosterone replacement has no detrimental effect on the restoration of the erectile mechanism after castration.

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### **Androgenic regulation of NO availability in rat penile erection.**

**Reilly CM, Zamorano P, Stopper VS, Mills TM.**

Department of Physiology and Endocrinology, Medical College of Georgia, Augusta 30912-3000, USA.

Prior studies from this laboratory, using untreated castrated (CASTRATE) rats and testosterone-treated castrated (TESTO) rats, have shown that the magnitude of the intracavernosal pressure increase during erection is androgen dependent. Studies from this and other laboratories have also presented evidence suggesting that penile erection is mediated principally by nitric oxide (NO). The present report was designed to confirm that androgens maintain the availability of cavernosal NO and to determine if this androgenic action is exerted at the genomic level modulating the expression of the neuronal form of the nitric oxide synthase gene (nNOS). The results showed that administration of supplemental L-arginine failed to augment the erectile response in either group, suggesting that substrate availability is not a cause of the reduced response in CASTRATE animals. Inhibition of NO synthesis with a nitro-arginine competitive inhibitor of nitric oxide synthase enzyme protein (NOS) resulted in strong inhibition of erection in both TESTO and CASTRATE rats. When given in conjunction with ganglionic stimulation to induce erection, the NO releasing drug,

sodium nitro-prusside (SNP), increased intracavernosal pressure in CASTRATE rats but not in TESTO rats, suggesting a deficiency of the available NO in CASTRATE-animals. Finally, reverse transcription-polymerase chain reaction (RT-PCR) demonstrated that mRNA levels for the enzyme nNOS in the penis were greater in TESTO animals than in CASTRATE rats. These results support the hypothesis that androgens mediate the erectile response in the rat penis by stimulating the expression of the neuronal isoform of nitric oxide synthase, thus maintaining an adequate supply of NO.

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### **The effects of testosterone on the cavernous tissue and erectile function.**

**Shabsigh R.**

College of Physicians & Surgeons, Columbia University, New York, NY 10032, USA.

A review of the current literature is conducted to explore the developmental aspects, animal and human experiences and the effects of pharmacological manipulation to explain the role androgens play in sexual function with special emphasis on erectile function and the erectile tissue. This review reveals that androgens are necessary for the normal development of the penis and their deficiency results in significant structural abnormalities. Although androgen receptors in the penis decrease after puberty, they usually do not disappear completely. Animal data show that androgens support erectile function through a direct effect on the erectile tissue. Experimental castration results in impaired erectile response to central and peripheral stimulation and decrease in penile tissue concentration of nitric oxide synthase-containing nerves.

Testosterone replacement reverses these abnormalities. In the rat penis, apoptosis is induced by castration and new DNA synthesis is induced by testosterone replenishment. Human data are less clear than animal data. Castration results in loss of libido and in erectile dysfunction. However, these effects are not universal. Testosterone enhances libido, frequency of sexual acts and sleep-related erections. Its effects on erotic erections are not clear.

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**Androgen-dependent nitric oxide release in rat penis correlates with levels of constitutive nitric oxide synthase isoenzymes.**

**Marin R, Escrig A, Abreu P, Mas M.**

Department of Physiology, School of Medicine, University of La Laguna, 38071 Tenerife, Spain.

Androgens are known to influence penile erection and nitric oxide synthase (NOS) activity in cavernosal tissue homogenates. The present study was an assessment of the effects of castration and androgen replacement on the *in vivo* release of nitric oxide (NO), and of the simultaneously recorded intracavernosal pressure (ICP) changes elicited by electrostimulation of the cavernosal nerves (SCN) in the anesthetized rat. The extracellular levels of NO in the corpora were monitored electrochemically using porphyrin microsenors. The content of NOS isoenzymes in corporal homogenates was determined by immunoblotting. The responses of castrated rats with or without testosterone (T) implants were compared to those of intact animals. Castration virtually abolished both the NO and the ICP responses to SCN. There was a concomitant significant decrease in the content of both the neuronal (nNOS) and the endothelial (eNOS) isoenzymes in the cavernosal tissue. All these effects of castration were prevented by T replacement. The NO response to SCN was positively correlated with the levels of nNOS and eNOS, especially when the values of the two isoforms were added ( $r = 0.71$ ,  $P < 0.001$ ). These data suggest that the facilitatory action of androgens on penile erection involves the up-regulation of both constitutive NOS isoenzymes in the corpora cavernosa.

**Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat.**

**Lugg JA, Rajfer J, Gonzalez-Cadavid NF.**

Department of Surgery, University of California at Los Angeles (UCLA) School of Medicine, Harbor-UCLA Medical Center, Torrance 90509.

Androgens are essential for the expression of normal libido in the male, but their role in the maintenance of the erectile response in humans is controversial. It has been shown previously in the rat that castration induces 1) loss of penile reflexes; and 2) considerable reduction in the erectile response to electric field stimulation (EFS) of the cavernosal nerve. Both of these effects can be reversed by testosterone replacement. The current study was performed to determine whether these testosterone effects are mediated via its conversion to dihydrotestosterone (DHT), and to what extent the synthesis of the mediator of penile erection, nitric oxide, is affected by castration and androgen replacement. Five-month-old rats were either castrated or left intact. The orchiectomized rats were implanted with SILASTIC brand silicon tubing (Dow Corning) containing testosterone or DHT with or without daily injections of the 5 alpha-reductase inhibitor finasteride. After 7 days, rats were submitted to EFS and the intracavernosal pressure was recorded. Castration reduced the EFS-induced erectile response by 50% in comparison with intact rats and testosterone restored this decrease to normal. When finasteride was given to these testosterone-treated castrate rats, erectile response was not restored. DHT was as effective as testosterone in restoring response to EFS in castrates and this effect was not decreased by finasteride. Nitric oxide synthase activity in the penile cytosol was measured by the arginine-citrulline conversion and was found to correlate with the EFS determinations. These results show that DHT is the active androgen in the prevention of erectile failure seen in castrated rats

and suggest that this effect may be mediated, at least partially, by changes in nitric oxide synthase levels in the penis.

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### **Regeneration of nitric oxide synthase-containing nerves after cavernous nerve neurotomy in the rat.**

**Carrier S, Zvara P, Nunes L, Kour NW, Rehman J, Lue TF.**

Department of Urology, University of California School of Medicine, San Francisco, USA.

In patients who recover erectile function after radical prostatectomy (with preservation of at least 1 neurovascular bundle), a recovery time of 6 to 18 months is not uncommon. As this is also the usual time required for regeneration of spinal nerves, we believe that regeneration of cavernous nerves, partially damaged inadvertently, may be responsible. In a rat model, we examined the long-term effect of unilateral and bilateral cavernous nerve transection on the nonadrenergic/noncholinergic (NANC) nervous system and erectile function. In 31 rats, nitric oxide synthase (NOS), the enzyme that catalyzes nitric oxide production was identified in penile nerve fibers from a mid-shaft segment with nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase staining and antibody to neuronal NOS. Animals were divided into three groups: 5 rats underwent pelvic exploration without transection of cavernous nerves (sham group); 13 rats underwent unilateral neurotomy of a 5-mm. segment of the cavernous nerve; and 13 rats underwent bilateral neurotomy. After bilateral ablation, the NOS-positive nerve fibers were significantly decreased at 3 weeks and remained so at 6 months; no erectile response could be elicited by pelvic nerve stimulation. After unilateral ablation, the NOS-positive nerve fibers were similarly decreased on the side of the neurotomy at 3 weeks, but by 6 months the number had increased significantly and approximated the level on the contralateral side. Furthermore, electrostimulation of the intact side induced a greater intracavernous pressure response at 6 months than at 3 weeks (N.B. the rat has an incomplete septum). Fibers positive for NOS were also identified

in the dorsal nerve. The staining pattern diminished as rapidly and significantly on the side of neurotomy as in tissue from the corpus cavernosum. However, regeneration was not seen. To our knowledge, this is the first demonstration of regeneration of NOS-containing nerves after cavernous nerve neurotomy. Our findings support the reports by others that unilateral nerve-sparing is sufficient to preserve erectile function.

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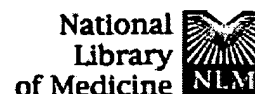
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**www.cymj.org****Role of nitric oxide in penile erection.****Jung HC, Mun KH, Park TC, Lee YC, Park JM, Huh K, Seong DH, Suh JK.**

Department of Urology, School of Medicine, College of Pharmacy, Yeungnam University, Taegu, Korea.

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**Baba K, Yajima M, Carrier S, Morgan DM, Nunes L, Lue TF, Iwamoto T.**

Department of Urology, University of California San Francisco, California, USA.

**OBJECTIVE:** To elucidate the effect of testosterone on penile innervation. **Materials and methods** Three groups of six rats each were assessed; two groups (1 and 2) were castrated and the third (group 3) underwent a sham operation (control). Eight weeks after castration, group 2 received a subcutaneous injection with testosterone. At 8 weeks, the rats in group 1 and 3 underwent a final functional analysis while those in group 2 did so at 12 weeks. The evaluation included a subcutaneous injection with apomorphine to study centrally mediated erection, and cavernosal nerve electrostimulation and papaverine injection to study peripherally mediated erection. At death a penile mid-shaft specimen was taken for NADPH-diaphorase staining. **RESULTS:** In the apomorphine study, castration resulted in significantly fewer yawns and erections than in the control, and those in group 2 significantly better central erectile function than in the controls. The mean (SEM) number of nitric oxide synthase (NOS)-containing nerve fibres in the corpora cavernosa and both dorsal nerves of castrated rats, at 46.2 (9.1) and 203 (32.1), respectively, were significantly lower than in rats in group 2, at 84.1 (11.2) and 300.6 (17.1), and than in the controls, at 88.6 (10.9) and 306.3 (22.9), respectively. The intracavernosal pressure decreased significantly in the absence of testosterone, both after electrostimulation and intracavernosal papaverine injection. However, there was no difference between the control and group 2 rats in either the number of NOS-containing nerve fibres or in the peripheral erectile functional study. **CONCLUSIONS:** Testosterone acts on the nervous system to mediate erection; when it is absent there may be down-regulation of both the production and activity of NO, thereby decreasing the response to peripheral stimulation via the NO pathway. The restoration of erectile function seen in rats in group 2 supports this phenomenon. Delayed testosterone replacement has no detrimental effect on the restoration of the erectile mechanism after castration.

PMID: 10792181 [PubMed - indexed for MEDLINE]

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☐ 4: J Androl 1997 Mar-Apr;18(2):110-5

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**Androgenic regulation of NO availability in rat penile erection.**

**Reilly CM, Zamorano P, Stopper VS, Mills TM.**

Department of Physiology and Endocrinology, Medical College of Georgia, Augusta 30912-3000, USA.

Prior studies from this laboratory, using untreated castrated (CASTRATE) rats and testosterone-treated castrated (TESTO) rats, have shown that the magnitude of the intracavernosal pressure increase during erection is androgen dependent. Studies from this and other laboratories have also presented evidence suggesting that penile erection is mediated principally by nitric oxide (NO). The present report was

designed to confirm that androgens maintain the availability of cavernosal NO and to determine if this androgenic action is exerted at the genomic level modulating the expression of the neuronal form of the nitric oxide synthase gene (nNOS). The results showed that administration of supplemental L-arginine failed to augment the erectile response in either group, suggesting that substrate availability is not a cause of the reduced response in CASTRATE animals. Inhibition of NO synthesis with a nitro-arginine competitive inhibitor of nitric oxide synthase enzyme protein (NOS) resulted in strong inhibition of erection in both TESTO and CASTRATE rats. When given in conjunction with ganglionic stimulation to induce erection, the NO releasing drug, sodium nitro-prusside (SNP), increased intracavernosal pressure in CASTRATE rats but not in TESTO rats, suggesting a deficiency of the available NO in CASTRATE-animals. Finally, reverse transcription-polymerase chain reaction (RT-PCR) demonstrate that mRNA levels for the enzyme nNOS in the penis were greater in TESTO animals than in CASTRATE rats. These results support the hypothesis that androgens mediate the erectile response in the rat penis by stimulating the expression of the neuronal isoform of nitric oxide synthase, thus maintaining an adequate supply of NO.

PMID: 9154504 [PubMed - indexed for MEDLINE]

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☐ 5: World J Urol 1997;15(1):21-6

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### **The effects of testosterone on the cavernous tissue and erectile function.**

**Shabsigh R.**

College of Physicians & Surgeons, Columbia University, New York, NY 10032, USA.

A review of the current literature is conducted to explore the developmental aspects, animal and human experiences and the effects of pharmacological manipulation to explain the role androgens play in sexual function with special emphasis on erectile function and the erectile tissue. This review reveals that androgens are necessary for the normal development of the penis and their deficiency results in significant structural abnormalities. Although androgen receptors in the penis decrease after puberty, they usually do not disappear completely. Animal data show that androgens support erectile function through a direct effect on the erectile tissue. Experimental castration results in impaired erectile response to central and peripheral stimulation and decrease in penile tissue concentration of nitric oxide synthase-containing nerves. Testosterone replacement reverses these abnormalities. In the rat penis, apoptosis is induced by castration and new DNA synthesis is induced by testosterone replenishment. Human data are less clear than animal data. Castration results in loss of libido and in erectile dysfunction. However, these effects are not universal. Testosterone enhances libido, frequency of sexual acts and sleep-related erections. Its effects on erotic erections are not clear.

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☐ 6: Biol Reprod 1999 Oct;61(4):1012-6

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### **Androgen-dependent nitric oxide release in rat penis correlates with levels of constitutive nitric oxide synthase isoenzymes.**

**Marin R, Escrig A, Abreu P, Mas M.**

Department of Physiology, School of Medicine, University of La Laguna, 38071 Tenerife, Spain.

Androgens are known to influence penile erection and nitric oxide synthase (NOS) activity in cavernosal tissue homogenates. The present study was an assessment of the effects of castration and androgen replacement on the in vivo release of nitric oxide (NO), and of the simultaneously recorded intracavernosal pressure (ICP) changes elicited by electrostimulation of the cavernosal nerves (SCN) in the anesthetized rat. The extracellular levels of NO in the corpora were monitored electrochemically

using porphyrin microsensors. The content of NOS isoenzymes in corporal homogenates was determined by immunoblotting. The responses of castrated rats with or without testosterone (T) implants were compared to those of intact animals. Castration virtually abolished both the NO and the ICP responses to SCN. There was a concomitant significant decrease in the content of both the neuronal (nNOS) and the endothelial (eNOS) isoenzymes in the cavernosal tissue. All these effects of castration were prevented by T replacement. The NO response to SCN was positively correlated with the levels of nNOS and eNOS, especially when the values of the two isoforms were added ( $r = 0.71$ ,  $P < 0.001$ ). These data suggest that the facilitatory action of androgens on penile erection involves the up regulation of both constitutive NOS isoenzymes in the corpora cavernosa.

PMID: 10491638 [PubMed - indexed for MEDLINE]

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☐ 7: Endocrinology 1995 Apr;136(4):1495-501

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**Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat.**

**Lugg JA, Rajfer J, Gonzalez-Cadavid NF.**

Department of Surgery, University of California at Los Angeles (UCLA) School of Medicine, Harbor-UCLA Medical Center, Torrance 90509.

Androgens are essential for the expression of normal libido in the male, but their role in the maintenance of the erectile response in humans is controversial. It has been shown previously in the rat that castration induces 1) loss of penile reflexes; and 2) considerable reduction in the erectile response to electric field stimulation (EFS) of the cavernosal nerve. Both of these effects can be reversed by testosterone replacement. The current study was performed to determine whether these testosterone effects are mediated via its conversion to dihydrotestosterone (DHT), and to what extent the synthesis of the mediator of penile erection, nitric oxide, is affected by castration and androgen replacement. Five-month-old rats were either castrated or left intact. The orchiectomized rats were implanted with SILASTIC brand silicon tubing (Dow Corning) containing testosterone or DHT with or without daily injections of the 5 alpha-reductase inhibitor finasteride. After 7 days, rats were submitted to EFS and the intracavernosal pressure was recorded. Castration reduced the EFS-induced erectile response by 50% in comparison with intact rats and testosterone restored this decrease to normal. When finasteride was given to these testosterone-treated castrate rats, erectile response was not restored. DHT was as effective as testosterone in restoring response to EFS in castrates and this effect was not decreased by finasteride. Nitric oxide synthase activity in the penile cytosol was measured by the arginine-citrulline conversion and was found to correlate with the EFS determinations. These results show that DHT is the active androgen in the prevention of erectile failure seen in castrated rats, and suggest that this effect may be mediated, at least partially, by changes in nitric oxide synthase levels in the penis.

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☐ 8: J Urol 1995 May;153(5):1722-7

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**Regeneration of nitric oxide synthase-containing nerves after cavernous nerve neurotomy in the rat.**

**Carrier S, Zvara P, Nunes L, Kour NW, Rehman J, Lue TF.**

Department of Urology, University of California School of Medicine, San Francisco, USA.

In patients who recover erectile function after radical prostatectomy (with preservation of at least 1 neurovascular bundle), a recovery time of 6 to 18 months is not uncommon. As this is also the usual time required for regeneration of spinal nerves, we believe that regeneration of cavernous nerves, partially damaged inadvertently, may be responsible. In a rat model, we examined the long-term effect of unilateral and bilateral cavernous nerve transection on the nonadrenergic/noncholinergic (NANC) nervous system and erectile function. In 31 rats, nitric oxide synthase (NOS), the enzyme that catalyzes nitric oxide production, was identified in penile nerve fibers from a mid-shaft segment with nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase staining and antibody to neuronal NOS. Animals were divided into three groups: 5 rats underwent pelvic exploration without transection

of cavernous nerves (sham group); 13 rats underwent unilateral neurotomy of a 5-mm. segment of the cavernous nerve; and 13 rats underwent bilateral neurotomy. After bilateral ablation, the NOS-positive nerve fibers were significantly decreased at 3 weeks and remained so at 6 months; no erectile response could be elicited by pelvic nerve stimulation. After unilateral ablation, the NOS-positive nerve fibers were similarly decreased on the side of the neurotomy at 3 weeks, but by 6 months the number had increased significantly and approximated the level on the contralateral side. Furthermore, electrostimulation of the intact side induced a greater intracavernous pressure response at 6 months than at 3 weeks (N.B. the rat has an incomplete septum). Fibers positive for NOS were also identified in the dorsal nerve. The staining pattern diminished as rapidly and significantly on the side of neurotomy as in tissue from the corpus cavernosum. However, regeneration was not seen. To our knowledge, this is the first demonstration of regeneration of NOS-containing nerves after cavernous nerve neurotomy. Our findings support the reports by others that unilateral nerve-sparing is sufficient to preserve erectile function.

PMID: 7536273 [PubMed - indexed for MEDLINE]

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☐ 9: J Urol 1997 Mar;157(3):1088-92

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**Age decreases nitric oxide synthase-containing nerve fibers in the rat penis.**

**Carrier S, Nagaraju P, Morgan DM, Baba K, Nunes L, Lue TF.**

Department of Urology, University of California School of Medicine, San Francisco 94143-0738, USA.

**PURPOSE:** To study the effect of aging on erectile function in a rat model. **MATERIALS AND METHODS:** We investigated: 1) the number and distribution of nerve fibers within the corpus cavernosum and dorsal nerve containing vasoactive intestinal polypeptide (VIP) and nitric oxide synthase (NOS); and 2) the erectile response to apomorphine (a central dopamine receptor agonist), electrostimulation of the cavernous nerve, and intracorporeal papaverine injection. **RESULTS:** The number of NOS-containing nerve fibers was significantly less in the old rats (24 months) than in the young (2.5 months) and intermediate (8.5 months)-aged ( $63.3 \pm 3.35$  vs.  $135.1 \pm 10.88$  [ $p < \text{or} = 0.0002$ ] and  $127.8 \pm 11.65$  [ $p < \text{or} = 0.0002$ ]). The number of erections induced by apomorphine was significantly less in the old rats than in the young ( $1.0 \pm 3.1$  vs.  $3.6 \pm 0.26$ ;  $p < 0.002$ ). With electrostimulation, the latency period before the onset of the intracavernous pressure rise was noted to increase with age ( $2.3 \pm 0.24$  sec. for the young vs.  $6.77 \pm 0.98$  sec. for the old,  $p < \text{or} = 0.0001$ ). The maximal intracavernous pressure after intracavernous papaverine injection decreased with age. **CONCLUSION:** The erectile mechanism appears to remain intact as rats age, but the response to central and peripheral stimulation decreases. The reduction in NOS-containing nerve fibers might account for these observations.

PMID: 9072549 [PubMed - indexed for MEDLINE]

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☐ 10: Neurosci Lett 1992 Aug 31;143(1-2):69-73

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**A possible neural source of nitric oxide in the rat penis.**

**Keast JR.**

Department of Physiology and Pharmacology, University of Queensland, St. Lucia, Australia.

NADPH diaphorase staining was used to indicate the presence of nitric oxide synthase (NOS) in whole mounts of rat major pelvic ganglion (MPG) and sections of rat penis. Many stained neurons were observed in the MPG and were distributed in a manner identical to that of retrogradely labelled penile neurons described previously. Staining was also observed within many axons of the penile (cavernous) nerve and in varicose terminals associated with various tissues of the penis. The results suggest that many, if not all, penile neurons of the MPG contain NOS and that a neural source of NO within the penis is likely.

PMID: 1436683 [PubMed - indexed for MEDLINE]

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☐ 11: J Androl 1995 Jan-Feb;16(1):2-4

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**The role of nitric oxide in erectile function.**

**Lugg JA, Gonzalez-Cadavid NF, Rajfer J.**

Department of Surgery, UCLA School of Medicine, Harbor-UCLA Medical Center, Torrance 90509, USA.

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### **Nitric oxide synthase gene therapy for erectile dysfunction: comparison of plasmid, adenovirus, and adenovirus-transduced myoblast vectors.**

**Tirney S, Mattes CE, Yoshimura N, Yokayama T, Ozawa H, Tzeng E, Birder LA, Kanai AJ, Huard J, de Groat WC, Chancellor MB.**

Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

**BACKGROUND AND PURPOSE:** Nitric oxide (NO) has been recognized as an important transmitter for genitourinary tract function. This transmitter mediates smooth muscle relaxation and is essential for erection. The objective of our research was to determine whether overexpression of nitric oxide synthase (NOS) in the corpus cavernosum of the penis would correct erectile dysfunction. **MATERIALS AND METHODS:** We introduced the inducible form of the enzyme NOS (iNOS) into the corpus cavernosum of adult (250-300 g) male Sprague-Dawley rats by injecting a solution of plasmid, adenovirus, or adenovirus-transduced myoblast cells (adeno-myoblast) (N = 3-5 each group). We also injected plasmid, adenovirus, and adeno-myoblast encoding the expression of the beta-galactosidase reporter gene. **RESULTS:** We noted expression of beta-galactosidase throughout the corpora cavernosum after injection of each of the three solutions. Staining was greatest for adeno-myoblast followed by adenovirus and then plasmid. The basal intracavernous pressure (ICP) of iNOS-treated animals (adenovirus and adenovirus-transduced myoblast) increased to  $55 \pm 23$  cm H<sub>2</sub>O v  $5 \pm 6$  cm H<sub>2</sub>O in naive animals ( $P = 0.001$ ). Stimulation of the cavernous nerve (15 Hz, 1.5 msec, 10-40 V, 1 min) resulted in a twofold increase in ICP (adenovirus and adeno-myoblast) from the basal level of the iNOS-treated animals. Direct in situ measurement of NO demonstrated release of 1 to 1.3  $\mu$ M NO in the adeno-myoblast-treated penis. **CONCLUSION:** Myoblast-mediated gene therapy was more successful in delivering iNOS into the corpus cavernosum than were the direct adenovirus or plasmid transfection methods. Gene therapy of NOS may open new avenues of treatment for erectile dysfunction. Control of NOS expression would be necessary to prevent priapism.

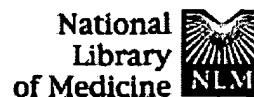
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## Gene therapy strategies for urological dysfunction.

Chancellor MB, Yoshimura N, Pruchnic R, Huard J.

Department of Urology, University of Pittsburgh School of Medicine, Suite 700 Kaufmann Building, 3471 Fifth Avenue, Pittsburgh, PA 15213, USA.  
chancellormb@msx.upmc.edu

Novel molecular techniques such as conventional and ex vivo gene therapy, and tissue engineering have only recently been introduced to the field of urology. The lower urinary tract is ideally suited for minimally invasive therapy, and also ex vivo approaches would limit the risk of systemic side effects. Muscle-derived stem cells have been used successfully to treat stress incontinence, and rats with diabetic bladder dysfunction benefited from nerve growth factor (NGF)-based gene therapy. Nitric oxide synthase and capase-7 might provide suitable gene therapy targets for erectile dysfunction and benign prostatic hyperplasia, respectively.

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- Review, Tutorial

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## Preliminary results of myoblast injection into the urethra and bladder wall: a possible method for the treatment of stress urinary incontinence and impaired detrusor contractility.

Chancellor MB, Yokoyama T, Tirney S, Mattes CE, Ozawa H, Yoshimura N, de Groat WC, Huard J.

Division of Urologic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

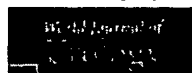
The purpose of this study is to explore the feasibility of myoblasts, the precursors of muscle fibers, injected periurethrally as a potential treatment of stress urinary incontinence. We also studied myoblast injection into the bladder wall to potentially improve detrusor contractility. A myoblast cell line was transduced with adenovirus carrying the expression of the beta-galactosidase reporter gene while in culture. The cells were incubated with fluorescent latex microspheres (FLMs) to follow the outcome of the injected cells. The tissue was harvested 3-4 days after injection; sectioned, fixed, assayed for beta-galactosidase expression, and counterstained with H+E. Photographs of the slides were taken under light and fluorescence microscopy. We have noted a large number of cells expressing beta-galactosidase and containing FLMs in the urethral and bladder walls under fluorescent microscopy (8 animals). Many regenerative myofibers expressing beta-galactosidase were also seen in the urethral and bladder walls. The fusion of injected myoblasts to form myotubes was seen in both the urethral and bladder walls. The introduction of myoblasts into the urethral and bladder wall is feasible and results in formation of myotubes and myofibers in the smooth muscle layers of the lower urinary tract. We hypothesize that myoblast injections can be used as a non-allergenic agent to enhance urethral closure and bladder function.

PMID: 10797585 [PubMed - indexed for MEDLINE]

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□ 3: World J Urol 2000 Feb;18(1):56-61

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### **Myoblast therapy for stress urinary incontinence and bladder dysfunction.**

**Yokoyama T, Huard J, Chancellor MB.**

Division of Urologic Surgery, University of Pittsburgh School of Medicine, Pennsylvania, USA.

The field of tissue engineering and gene therapy has an exciting and promising future. During the past few years we have begun a comprehensive effort to investigate the use of myoblasts to improve and expand the treatment of stress urinary incontinence and bladder dysfunction. Moreover, we can expect the application of myoblast-mediated ex vivo gene transfer in the field of urology. In this paper we discuss the compositions of and methods involving the use of myogenic or muscle-derived cells for tissue engineering and cell-mediated gene therapy.

PMID: 10766045 [PubMed - indexed for MEDLINE]

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